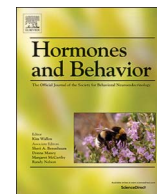




Contents lists available at ScienceDirect

## Hormones and Behavior

journal homepage: [www.elsevier.com/locate/yhbeh](http://www.elsevier.com/locate/yhbeh)

## Endocrine active metals, prenatal stress and enhanced neurobehavioral disruption

Marissa Sobolewski\*, Katherine Conrad, Elena Marvin, Joshua L. Allen, Deborah A. Cory-Slechta

Dept. of Environmental Medicine, University of Rochester School of Medicine, Rochester, NY, United States

## ARTICLE INFO

## Keywords:

Metals  
Lead  
Methylmercury  
Arsenic  
Prenatal stress  
Corticosterone  
Behavior

## ABSTRACT

Metals, including lead (Pb), methylmercury (MeHg) and arsenic (As), are long-known developmental neurotoxicants. More recently, environmental context has been recognized to modulate metals toxicity, including nutritional state and stress exposure. Modulation of metal toxicity by stress exposure can occur through shared targeting of endocrine systems, such as the hypothalamic-pituitary-adrenal axis (HPA). Our previous rodent research has identified that prenatal stress (PS) modulates neurotoxicity of two endocrine active metals (EAMs), Pb and MeHg, by altering HPA and CNS systems disrupting behavior. Here, we review this research and further test the hypothesis that prenatal stress modulates metals neurotoxicity by expanding to test the effect of developmental As  $\pm$  PS exposure. Serum corticosterone and behavior was assessed in offspring of dams exposed to As  $\pm$  PS. PS increased female offspring serum corticosterone at birth, while developmental As exposure decreased adult serum corticosterone in both sexes. As + PS induced reductions in locomotor activity in females and reduced response rates on a Fixed Interval schedule of reinforcement in males, with the latter suggesting unique learning deficits only in the combined exposure. As-exposed males showed increased time in the open arms of an elevated plus maze and decreased novel object recognition whereas females did not. These data further confirm the hypothesis that combined exposure to chemical (EAMs) and non-chemical (PS) stressors results in enhanced neurobehavioral toxicity. Given that humans are exposed to multiple environmental risk factors that alter endocrine function in development, such models are critical for risk assessment and public health protection, particularly for children.

## 1. Introduction

Studies examining the impact of environmental chemical exposures on endocrine systems typically focus on xenobiotics included in personal care or other consumer products, such as BPA and phthalates, as well as, brominated flame retardants, perchlorates etc. Far less consideration has been given to the fact that many metals are endocrine disruptors (Dyer, 2007; Iavicoli et al., 2009; Kortenkamp, 2010), despite the fact that exposure of children to heavy metals, including lead (Pb), arsenic (As) and mercury (Hg), remains an intractable public health problem. As seen in Flint, Michigan and other cities around the United States, children are continuously exposed to metals, particularly through drinking and food sources. Lead has been a chronic problem in the United States with many children presenting with blood leads higher than 5  $\mu\text{g}/\text{dL}$  (DeWitt, 2017; Hanna-Attisha et al., 2016; Shah et al., 2017) and over a 100 million people are exposed to elevated levels of arsenic ( $> 10 \mu\text{g}/\text{L}$ ) through drinking sources, including well water (Bommarito et al., 2017; Organization, 2004; Rager et al., 2017;

Wasserman et al., 2004; Wasserman et al., 2016). A significant public health concern surrounding metal exposure relates to their potential to produce cognitive deficits (Canfield et al., 2004; Debes et al., 2016; Jeong et al., 2017; Lanphear et al., 2005; Wasserman et al., 2016). Pb exposure specifically is associated with reductions in IQ, learning, and attention deficits in human cohorts and these findings are paralleled in animal models, effects considered to derive from their actions on brain mesocorticolimbic circuits (i.e., prefrontal cortex, nucleus accumbens, hippocampus) (Canfield et al., 2003; Cohn et al., 1993; Jett et al., 1997; Lanphear et al., 2005; Schneider et al., 2016). As exposure has been associated with neurobehavioral disorders, including attention and cognitive function, with domains differing slightly between males and females (Rodriguez-Barranco et al., 2013; Rosado et al., 2007; Wasserman et al., 2004; Wasserman et al., 2016). MeHg exposure has been associated with neurodevelopmental delays, although co-occurring beneficial micronutrients including n-3 polyunsaturated fats (PUFAs) may modulate such effects (Cohen et al., 2005; Dzwilewski and Schantz, 2015; Myers and Davidson, 1998; Wang et al., 2014). The

\* Corresponding author at: Box EHSC, University of Rochester Medical Center, Rochester, NY 14642, United States.  
E-mail address: [marissa\\_sobolewski@urmc.rochester.edu](mailto:marissa_sobolewski@urmc.rochester.edu) (M. Sobolewski).

<https://doi.org/10.1016/j.yhbeh.2018.01.004>

Received 28 September 2017; Received in revised form 5 January 2018; Accepted 14 January 2018  
0018-506X/ © 2018 Elsevier Inc. All rights reserved.

potential combinatorial effect of nutrients and MeHg exposure on cognition provides evidence that developmental environments may modulate metal neurotoxicity. In fact, it is becoming increasingly clear that environmental context may modulate the neurotoxic effects of a broad range of endocrine disrupting chemicals (Crews et al., 2003; Pottinger, 2003).

In the human environment, numerous risk factors exist with the potential to contribute to cognitive impairments in children, such as prenatal stress (PS), the effects of which may be more detrimental, in combination with metals exposure. The shared occurrence of risk factors are not equally distributed, as the highest blood Pb levels are often found in children of low socioeconomic status (SES) (Bellinger et al., 1988; Tsoi et al., 2016; White et al., 2016) and the same populations are repeatedly exposed to resource deprivation, both material and social, as well as dangerous neighborhood conditions, violence and racism (Keenan et al., 2007; Thayer and Kuzawa, 2014). In the context of human health, stress is a component of virtually every individual's life, which can be broadly viewed as psychosocial, environmental or physical challenges to which the body responds through activation of the hypothalamic-pituitary-adrenal (HPA) axis and production of hormonal and neurotransmitter mediators. Via inputs to hippocampus and amygdala in brain, stressors activate the HPA axis, leading to release of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus. These act on the anterior pituitary to stimulate the release of adrenocorticotrophic hormone (ACTH), then triggering release of glucocorticoids from adrenal cortex (Fig. 1). Cortisol is the major human glucocorticoid and corticosterone plays the primary role for rodents. Via a negative feedback system, glucocorticoids act on pituitary, hypothalamus and hippocampal glucocorticoid receptors (GR) to terminate the HPA stress response. This chemical signaling produces a coordinated physiological response that restores homeostasis. HPA activation clearly conveys important developmental coordination and survival benefits to an organism. However, problems ensue in cases of allostatic overload or HPA axis dysregulation, including failure of the negative feedback, inadequate stimulation, or delayed recovery. Disruption of HPA axis function has been associated with a variety of human diseases and disorders (Denhardt, 2018; Juster et al., 2016; Korte et al., 2005; Lupien et al., 2009; McEwen, 2000; McEwen, 2017; Peters et al., 2017; Shonkoff et al., 2009; Stavrou et al., 2017). The cognitive deficits induced by exposure to endocrine active metals (EAMs) arise partially through disruptions in HPA axis function and mesocorticolimbic (MESO) circuitry, both systems critical to mediation of rewarding properties of stimuli and to executive/cognitive functions (Fig. 1). These two systems

are interconnected. For example, products of HPA activation, such as corticosterone, increase dopamine signaling in the nucleus accumbens (Graff and Tsai, 2013), which in turn is critical for conditioning processes (Cory-Slechta et al., 1997). Microinjection of the dopamine D2 receptor antagonist, sulpiride, into medial PFC of rats attenuates glucocorticoid-induced impairment of long-term memory retrieval (Pakdel and Rashidy-Pour, 2007). Cortisol administration to humans has been shown to downregulate activity of striatum in both reward and non-reward conditions (Montoya et al., 2014). Prenatal exposure to glucocorticoids during late gestation in rats changed the shape and volume of the midbrain dopamine cell bodies and size of dopaminergic neurons and astrocytes within these nuclei, and also altered their target innervation density and neurochemical transmitter functions, effects which were also profoundly sexually-dimorphic (Gillies et al., 2016). Indeed, gestational exposures to glucocorticoids have been reported to program brain dopamine circuitry (Rodrigues et al., 2011). Metals exposure disrupts behaviors mediated by brain mesocorticolimbic systems (Cory-Slechta et al., 1998; Cory-Slechta et al., 1997; Cory-Slechta et al., 1996; Evans and Cory-Slechta, 2000); as both Pb and MeHg alter learning under a fixed interval (FI) schedule of food reward (Cory-Slechta et al., 1996; Virgolini et al., 2008a; Weston et al., 2014a). Pb, As, and MeHg have been shown to impact MESO dopamine function (Amos-Kroohs et al., 2016; Boomhower and Newland, 2017; Castoldi et al., 2006; Dreiem et al., 2009; Moreno Avila et al., 2016; Srivastava et al., 2016; Stansfield et al., 2015; Wu et al., 2017; Zuch et al., 1998).

Given the critical role of HPA and MESO systems in cognitive deficits associated with metals exposure, prenatal stress (PS) may modulate a broad range of metals neurotoxicity. In fact, numerous metals, including As, Hg, Au, and Cd, have mechanistically been shown to alter HPA physiology including direct action on glucocorticoid receptor binding or activity (Brkljacic et al., 2004; Elez et al., 2001; Makino et al., 1996; Spuches and Wilcox, 2008). EAMs alter levels of steroid hormones along the HPA axis in human studies and animal models (Appleton et al., 2017; Barros et al., 2004; Berger et al., 2002; Bodwell et al., 2006; Braun et al., 2014; Caldwell et al., 2015; Cory-Slechta et al., 1998; Cory-Slechta et al., 1999; Davey et al., 2007; Desaulniers et al., 2013; Haider et al., 2013; Martinez-Tellez et al., 2009; Rossi-George et al., 2011; Rothenberg et al., 2016; Souza-Talarico et al., 2017; Virgolini et al., 2008a). In fact, developmental exposure to EAMs, Pb, MeHg, and As, produce protracted, lifelong HPA axis dysregulation. For example, exposure to 8 mg/kg MeHg on GD15 increased corticosterone levels 4-fold in male rat offspring measured after 90 days of age (Carratu et al., 2008). In addition, 2-fold increases in corticosterone and in ACTH were found after only 5 ppb MeHg in drinking water exposures

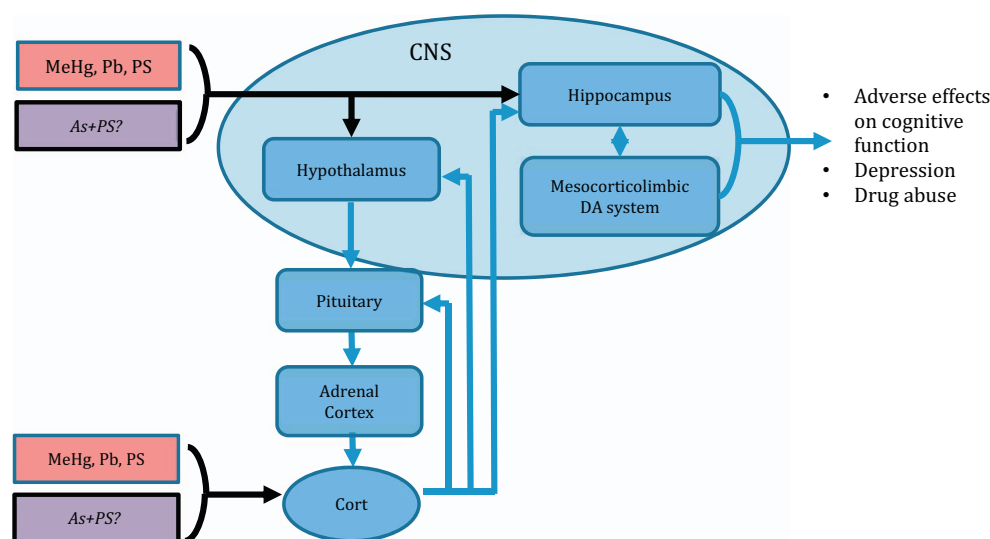


Fig. 1. Both Pb and MeHg and stress activate the HPA axis and act on brain hippocampal and mesocorticolimbic dopamine/glutamate systems. Thus, they share multiple common biological substrates, and effects of Pb are enhanced by stress. Does As also interact with PS to alter the HPA axis, act on hippocampal and mesocorticolimbic systems with similar effects on behavior?

Download English Version:

<https://daneshyari.com/en/article/6793813>

Download Persian Version:

<https://daneshyari.com/article/6793813>

[Daneshyari.com](https://daneshyari.com)